(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 115 627 A1

BEST AVAILABLE COPY

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 83113070.3

(51) Int. Cl.³: A 61 K 37/02

(22) Date of filing: 23.12.83

PHARMACEUTICAL
~~PHARM~~ COMPSN. CONTG. CALCITONIN AND SURFACTANT + FOR PROLONGED INTRANASAL ADMIN. WITH BONE METABOLISM DISORDERS

(30) Priority: 29.12.82 US 454128

(43) Date of publication of application: 15.08.84 Bulletin 84/33

(84) Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: Armour Pharmaceutical Company, 303 South Broadway, Tarrytown New York 10591 (US)

(72) Inventor: Mufson, Daniel, 24 Hillside Drive, Thiells, N.Y. (US)
Inventor: Hanson, Musetta A., 1 Consulate Drive, Tuckhoe, N.Y. (US)

(74) Representative: Patentanwälte Grünecker, Dr. Kinkeldey, Dr. Stockmair, Dr. Schumann, Jakob, Dr. Bezold, Meister, Hilgers, Dr. Meyer-Plath, Maximilianstrasse 58, D-8000 München 22 (DE)

(54) Enhancement of intranasal absorption of calcitonin by formulation with surfactants.

(57) A pharmaceutical composition for the treatment of disorders of bone metabolism which comprises an aqueous or non-aqueous medium suitable for intranasal administration and containing a therapeutically effective amount of calcitonin and a surface active agent.

563

202637

EP 0 115 627 A1

ENHANCEMENT OF INTRANSAL ABSORPTION OF CALCITONIN BY FORMULATION WITH SURFACTANTS

The present invention relates to a novel method of administering calcitonin to patients and to formulations adapted for nasal adminstration.

Calcitonin is a polypeptide hormone isolated from different organs in different species, including man and salmon, or obtained via synthetic routes. Calcitonin is recognized as being effective in diminishing hypercalcemia and decreasing plasma phosphate concentrations in patients with hyperparathyroidism, idiopahtic hypercalcemia of infancy, vitamin D intoxication, and osteolytic bone metastases. While direct renal effects and actions on the gastrointestinal tract are recognized, calcitonin is best known for its effect on bone. Its use has proved to be effective in diseases characterized by increased skeletal resorption and abnormal bone formation, such as occurs for example, in Paget's disease.

The method of administration of calcitonin is predominantly by injection, although efforts were made in the prior art to use other modes of administration, especially for the treatment of localized conditions. While injectable administration by physicians of calcitonin is proper for short-term therapy, administration of calcitonin by injection to patients in need of long-term calcitonin therapy has a serious problem. Not only is it costly to patients to have physicians do the administration of calcitonin for extended periods of time but it is also painful and inconvenient. Nor

564

can calcitonin be given orally to patients as it will be destroyed by the digestive juices in the gastrointestinal tract.

In view of the foregoing, it is apparent that a serious need exists for a different route of delivery of calcitonin to patients suffering from conditions that require prolonged calcitonin therapy.

Nasal preparations are known in the prior art. Generally, nasal preparations comprise an oil-in-water or water-in-oil emulsion or an oily solvent base suitable for use on the mucous membranes, such as mineral or vegetable oils and fatty acid esters and one or more chemicals which are soluble in the base. Such preparations usually contain one or more active drugs intended to alleviate or mitigate a condition in the body by their adsorption into the blood stream through the mucous membrane of the nose.

While small molecules such as propranolol are efficiently absorbed intranasally, large molecules such as calcitonin show little if any absorption. The purpose of this invention is to find agents capable of increasing the bioavailability of calcitonin so that cost of therapy is reasonable. The prior art has also recognized that the nasal absorption of certain drugs may be facilitated by the use of surfactants in such nasal preparation. For example, insulin and polypeptides were found to have an improved absorption rate when used in a solution containing a surfactant.

It has now been found that hypercalcemia, Paget's disease and other disorders of bone metabolism can be advantageously treated by intranasal application of calcitonin contain in a nasal preparation having an absorption promoter and a buffer as essential ingredients. Such preparations possess enhanced absorption across the nasal mucosa when applied intranasally, but causes no irritation or discomfort on extended use.

The present invention relates to a method for the treatment of a mammal suffering from a disorder characterized by high serum calcium which comprises intranasal application of a nasal preparation containing a peptide having calcitonin activity and an absorption promoting agent to effect control of said disorders by transephlithelial action.

According to the invention, calcitonin is intranasally administered to a mammal via a novel dosage form, such as a solution, ointment, or gel.

Calcitonin is a peptide hormone of 32 amino acids with a disulfide bond at 1-7 in the amino terminus of the molecule. These first seven amino acids with the disulfide bond seem essential for activity and this sequence is preserved from species to species. Calcitonin, as used herein, means not only peptides having a structure corresponding to one of the naturally occuring hormones, and which may be naturally or synthetically produced, but also related peptides having calcitonin activity.

The amount of calcitonin contained in the preparation of the present invention may vary according to various parameters, such as the nature of the preparation,

the particular kind or activity of calcitonin employed and the condition or ailment to be treated with the preparations. In general, the concentrations are somewhat higher than those found in compositions for the systemic administration of calcitonin. It has been found that a concentration level of 1 to 150 micrograms per ml and preferably 2 to 30 micrograms per ml achieve the desired result. The levels of administration of calcitonin also vary somewhat from those used systemically. In the case of human patients, for example, amounts of from 0.7 to 70 micrograms, particularly from 1 to 25 micrograms, are usually appropriate for single dosages given and repeated as often as the physician finds it necessary and such dosages correspond generally to about 0.01 to 1 micrograms, and particularly 0.03 to 0.35 micrograms, per kilogram of body weight. (The above concentration and dosage levels of calcitonin apply to calcitonin with a potency of about 4000 International Units per mg and may be adjusted pro rata for calcitonin of other potencies.)

The diluent base or vehicle used in accordance with the present invention may be non-aqueous or aqueous. In the former case the group of diluents is the physiologically acceptable polar solvents. Preferred compounds of this type are those with which it is possible to make a solution of adequate concentration of dissolved calcitonin. Examples of these compounds include dimethylsulphoxide, dimethyl foramide, dimethyllauramide, polyhydroxy alcohols, vegetable and mineral oils. If desired, such non-aqueous media may be mixed with water to form the diluent of the preparation.

However, the degree of physiological acceptabliity of the non-aqueous diluents is generally less than that of aqueous media and the preferred diluent is therefore water without the addition of organic solvents.

In the preparations of the present invention, calcitonin is used in combination with an absorption promoter. Such absorption promoters include the physiologically acceptable surface active agents. The amount of such an agent may be in the range from about 0.01 to about 10% w/v or higher and preferably about 0.05 to about 1.0% w/v, the amount depending on the specific surfactant used. The amount is generally kept as low as possible since above a certain level no further enhancement of absorption can be achieved and also too high of a surfactant level may cause irritation of the nasal mucosa. Such surface active agents include:

a. Bile salts, such as sodium taurocholate, sodium cholate, sodium deoxycholate and sodium glycholate;

b. Cationics, such as the long chain amine condensates with ethylene oxide and quaternary ammonium compounds, for example cetyl trimethyl ammonium bromide and dodecyl dimethyl ammonium bromide;

c. Antonics, such as alkylbenzenesulfonates, N-acyl-n-alkyltaurates, α -olefin sulfonates, sulfated linear primary alcohols and sulfated polyoxyethylenated straight-chain alcohols;

d. Nonionics, such as polyoxyethylenated alkylphenols, polyeoxethylenated straight chain alcohols, long chain carboxylic acid esters including glycerol ester of natural fatty acids, propylene glycol, sorbitol, and polyoxyethylenated sorbitol esters;

e. Amphoterics, such as imidazoline carboxyslates, sulfonates and the like; and

f. Phospholipids, such as phosphotidyl choline and the like.

The preparations of the present invention preferably contain a phosphate or acetate buffer in the range of 0.01 M to 0.5 M and preferably in the range of 0.05 M to 0.2 M. This concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle.

The preparations of the present invention may also contain other additives, such antioxidants, stabilizers, tonicity adjusters, viscosity builders, preservatives, and the like. The concentration of these additives may vary according to the particular additive used and the desired result sought. In general, the concentrations for these additives will be in the range as follows:

Additives	% W/V
Antioxidants	0.01 - 0.2
Stabilizers	0.01 - 2.0
Tonicity Adjuster	0.01 - 0.5
Viscosity Builders	0.1 - 2.0
Preservatives	0.001 - 2.0

While the use of the kind and concentration of additives will be well within the ability of the skilled artisan, the following will serve as illustration for two additives generally used in pharmaceutical preparations intended for similar purposes.

569

202637

Preservatives	% W/V
Benzalkonium chloride	0.004 - 0.02
Disodium Ethylene Diamine Tetraacetate	0.01 - 0.2
Thimerosal	0.001 - 0.01
Chlorobutanol	0.5 - 1.0
Methyl and/or Propyl Paraben	0.01 - 0.2
Phenethyl Alcohol	0.25 - 0.75
Cyclohexedine	0.01 - 0.1

Viscosity Agents	% W/V
Methyl Cellulose	0.1 - 2.0
Hydroxyethyl Cellulose	0.1 - 2.0
Hydroxypropyl Cellulose	0.1 - 2.0
Polyvinylprrolidone	0.5 - 2.0

In preparing the formulations of the present invention, calcitonin is dissolved in the vehicle or dilutent after which the additional ingredients are added in accordance with customary formulation procedures known in the pharmaceutical industry.

Examples of typical intranasal formulations are set forth below. However, it is to be understood that these examples are given by way of illustration only and are not to be construed as limiting the invention either in spirit or in scope as many modifications will be apparent to those skilled in the art.

570

202637

0115627

EXAMPLE 1	% W/V
Calcitonin	0.009
Sodium Taurocholate	0.5
Gelatin	1.0
Purified Water Q.S.	100

EXAMPLE 2	% W/V
Calcitonin	0.009
Miranol C2M	1.0
Gelatin	1.0
Purified Water Q.S.	100

EXAMPLE 3	% W/V
Calcitonin	0.009
Miranol C2M	0.05
Sodium Acetate $.3H_2O$	1.36
Acetic Acid	0.6
Purified Water Q.S.	100

EXAMPLE 4	% W/V
Calcitonin	0.009
Polysorbate 80	1.0
Sodium Acetate $.3H_2O$	1.36
Acetic Acid	0.6
Purified Water Q.S.	100

571

202637

0115627

EXAMPLE 5	% W/V
Calcitonin	0.003
Brij 30	1.0
Sodium Acetate $.3H_2O$	1.36
Acetic Acid	0.6
Purified Water Q.S.	100

EXAMPLE 6	% W/V
Calcitonin	0.009
Myrj 59	1.0
Sodium Acetate	1.36
Acetic Acid	0.6
Purified Water Q.S.	100

EXAMPLE 7	% W/V
Calcitonin	0.009
Miranol C2M	1.0
Sodium Phosphate	2.40
Citric Acid	0.34
Thimerasol	0.002
Purified Water Q.W.	100

572

202637

0115627

EXAMPLE 8	% W/V
Calcitonin	0.009
Sodium Taurocholate	0.5
Sodium Acetate .$3H_2O$	1.36
Acetic Acid	0.6
Benzalkonium Chloride	0.01
DiSodium ethylenediame tetraacetate	0.1
Purified Water Q.S.	100

EXAMPLE 9	% W/V
Calcitonin	0.009
Sodium Taurocholate	0.5
Sodium Acetate .$3H_2O$	1.36
Acetic Acid	1.36
Chlorobutanol	0.1
Phenethyl Alcohol	0.2
Purified Water Q.S.	100

EXAMPLE 10	% W/V
Calcitonin	0.003
Miranol C2M	1.0
Sodium Phosphate	2.40
Citric Acid	0.34
Thimerasol	0.002
Purified Water Q.S.	100

573

202637

The gelatin used in the above formulations is a standard hydrolipid animal gelatin prepared for pharmaceutical use and routinely used as a diluent for peptides.

According to the present invention, it has been found that calcitonin can be administered intranasally from a vehicle containing absorption promoters with results considerably superior to those obtained with the administration of calcitonin without absorption promoters. The following studies were undertaken to examine the bioavailability of calcitonin from the formulations of the presetn invention, dependency of intranasal absorption of calcitonin on the level of absorption promoters and stability of calcitonin in the presence of absorption promoters.

PROTOCOL

Male rats weighing 150-250 g were weighed and anesthetized with sodium pentobarbital, 50/mg/kg. by intraperitoneal injection. Once anesthetized the nasopalatine process was occluded with glue. The animals were randomly placed into groups of 5-7 rats with the number of groups being dependent upon the number of intranasal formulations to be tested. Supplemental pentobarbital anesthesia was administered as necessary throughout the study.

Prior to administration of the test material, blood was collected by cardiac puncture using a 25G 5/8" needle. Fifty (50) microliters of the salmon calcitonin-containing surfactant solution was then instilled into the nasal septum using polyethylene tubing (PE 20, Peterson Technics, Monmouth Junction, N.J.) connected to a 1 ml syringe; the tubing was inserted about 1 cm into the nasal septum. One and three

hours after nasal instillation, blood was again collected by cardiac puncture.

Biochemical Analysis

Blood samples were allowed to clot at room temperature and were then refrigerated for 30-60 minutes to provide maximum clot retraction. The samples were centrifuged at 4°C., 5000 rpm for 10 minutes (Beckman Model J2-21 Centrifuge, Beckman Instruments, Palo Alto, CA). Serum calcium was quantitated using a Calcette (Model 4008, Precision Systems, Sudbury, MA).

Data Analysis

Serum calciumvalues at 0, 1 and 3 hours were expressed as mean ± standard deviation. In addition, the absolute change and the percent change from the pretreatment (0 time) value at 1 and 3 hours was also calculated. Statistical analysis consisted of comparison of the serum calcium values at 0 and 1 hour, 0 and 3 hours, and 1 and 3 hours using a t test.

EXAMPLE 11

This example illustrates decrease in serum calcium in blood samples obtained in accordance with the above protocol when: a. calcitonin is administered alone; b. calcitonin is administered in formulations containing various absorption promoters; and c. no calcitonin is present in the formulations.

Table 1 shows the result obtained.

202637

576

TABLE I

Calcitonin U/kg body weight vehicle/surfactant	TIME AFTER DOSE 0 hour mg/dl	1 hour mg/dl.	% decr.	3 hour mg/dl	% decrease
2U 1% gel -	8.8	9.5	NONE	9.9	NONE
5U 1% gel -	8.5	7.9	7.1	9.5	NONE
10U 1% gel -	9.2	7.6	17.4	9.7	NONE
10U .1M Acetate -	8.8	6.3	28.4	9.0	NONE
- 1% gel 1% Miranol C2M(1)	8.9	8.8	NONE	9.2	NONE
- 1% gel 1% Taurocholate	9.1	9.5	NONE	9.8	NONE
3U 1% gel 1% Miranol C2M(1)	8.9	6.7	24.7	7.6	14.6
	8.8	6.5	26.1	8.5	3.4
	8.7	6.8	21.8	8.9	2.3
3U 0.1M Acet. 1% Miranol C2M(1)	8.7	6.8	21.8	8.9	2.3
10U 1% gel 1% Miranol C2M(1)	9.5	6.1	35.8	8.8	7.4
	9.1	7.5	17.6	6.6	27.5
	8.9	7.1	20.2	7.1	20.2
10U 0.1M Acet. 1% Miranol C2M(1)	9.3	6.1	34.4	6.5	30.1
	9.2	6.8	26.1	8.4	8.7
3U 1% gel 1% Taurocholate	9.1	7.0	23.1	6.4	29.6
10U 1% gel 1% Taurocholate	9.3	7.1	23.7	6.3	32.3
	8.6	6.1	29.1	5.9	31.4
10U 0.1M Acet. 1% Taurocholate	9.1	6.5	28.6	5.7	37.4
3U 1% gel 1% Tween 80 (Polysorbate 80)	8.3	6.2	25.3	8.7	NONE
	8.9	7.1	20.2	9.2	NONE

(1) Dicarboxylated fatty imidazoline or dicarboxylic coconut derivative.

572
2026637
0115627

578
202637
0115627

TABLE I (Cont'd.)

Calcitonin U/kg body weight vehicle/surfactant	TIME AFTER DOSE 0 hour mg/dl	1 hour mg/dl.	1 hour % decr.	3 hour mg/dl	3 hour % decrease
10U 1% gel 1% Tween 80 (Polysorbate)	8.7	6.6	24.2	7.3	16.1
	8.9	6.7	24.7	8.4	5.6
3U 1% gel 0.5% Benzal-konium Chloride	8.7	5.9	32.2	6.3	27.6
	8.9	6.5	26.9	9.0	NONE
10U 1% gel 0.5% Benzal-konium Chloride	8.5	7.2	15.3	7.9	7.1
	9.0	6.0	33.3	6.2	31.0
3U 1% gel 1% Saponin (Sapogin Glycoside)	8.6	7.3	15.1	7.3	15.1
10U .1M Acet. 1% NaL Saf	8.7	6.5	25.9	8.1	6.9
10U .1M Acet. 1% Brij 30 (Polyoxyethylene (4) lauryl ether)	8.7	6.5	25.9	6.5	25.9
10U .1M Acet. 1% Myrj 59 (Polyoxyethylene (100) Stearate)	8.5	6.2	27.1	8.4	1.2
10U .1M Acet. 1% Tween 80	8.7	7.5	13.8	7.1	18.4
10U .1M Acet. 1% Aer OT (Sodium dioctyl sulfosuccinate)	9.1	6.6	27.5	7.6	16.5

0115627

EXAMPLE 12

This example illustrates that the enhancement of intranasal absorption depends on the level of absorption promoter present in the formulation.

Table II shows the result obtained.

202637

579

0115627

TABLE II

10U Calcitonin/kilo in 0.1M Acetate with	0 hour mg/dl	1 hour mg/dl	1 hour %	3 hour mg/dl	3 hour %
1% Taurocholate	9.1	6.5	28.6	5.7	37.4
0.5% "	9.0	6.1	32.2	7.5	16.6
0.25% "	9.1	6.8	25.3	7.4	18.2
0.1% "	8.9	6.5	27.0	8.3	6.7
0.05% "	9.0	7.6	15.5	8.7	3.3

10U calcitonin/kilo in 0.1M Acetate with

1% Miranol C2M (dicarboxylic coconut derivative, sodium salt)

0.5% "

0.25% "

0.1% "

0.5% "

580

202637

0115627

EXAMPLE 13

This example illustrates that calcitonin maintains its activity level in the formulations of the present invention on storage at room temperatures.

Table III shows the results obtained.

202637

581

0115527

TABLE III

10U calcitonin in 1% gel with 1% Nirunol C2M	0 hour mg/dl	1 hour mg/dl	1 hour %	3 hour mg/dl	3 hour %
initial	8.9	7.1	20.2	7.1	20.2
2 wks @ RT	9.1	7.2	20.9	6.4	29.7
4 wks @ RT	9.1	6.0	34.1	6.9	24.2
10U calcitonin in 1% gel with 1% Tween 80 (Polysorbate 80)					
initial	8.9	6.7	24.7	8.4	5.6
2 wks @ RT	8.8	6.7	23.9	8.3	6.0
4 wks @ RT	8.8	6.3	28.4	6.7	23.9

202637

European Patent Office

EUROPEAN SEARCH REPORT

0115627 Application number

EP 83113070.3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	US - A - 4 241 051 (CHRISTIE et al.) * Claims 3,4,5,7-10; column 1, line 45 - column 4, line 46 *	1,6	A 61 K 37/02
A	GB - A - 1 548 984 (CIBA-GEIGY AG) * Claims, especially claim 5; page 1, line 9 - page 3, line 66 *	1,2,5	
A	DE - A1 - 2 254 061 (HOECHST AG) * Claim 1,4; pages 1,2 *		

584

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 K 37/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	30-03-1984	STÖCKLMAYER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503. 03.82

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.